<u>REMARKS</u>

Claims 1-5, 8-11, 14-17, 20-23, 26-29, 32-35, and 37-39 are presented for examination, claims 6, 7, 12, 13, 18, 19, 24, 25, 30, 31, and 36 having been withdrawn from consideration. Claims 1, 8, 14, 20, 26, and 32 are independent.

Applicants amend claims 1, 8, 14, 20, 26, and 32 herein to better claim the invention. No new matter is added. Support for the amendments may be found throughout the Specification and Figures as originally filed, and specifically in the Specification at page 34 (e.g., steps 614 et seq.). Applicants respectfully urge that the pending claims are in condition for allowance.

I.   **Claim Rejections under 35 U.S.C. §103(a)**

In the Office Action:

claims 1-5, 8-11, 14-17, 20-23, 26-29, and 32-35 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro et al., Omics: A Journal of Integrative Biology, Vol. 7, No. 4, 2003 (hereafter "Sauro") in view of Kurata et al., Nucleic Acids Research, Vol. 31, No. 14, p.4071-4084, 2003 (hereafter "Kurata") in view of Funhashi et al., Biosilico, Vol. 1 No. 3, pp. 159-162, November 2003 (hereafter "Funhashi") and further in view of International Application Publication No. WO 96/22575 to Thalhammer-Reyo (hereafter "Thalhammer-Reyo") (See the Office Action, pages 4-5);

claims 37-39 was rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro, Kurata, Funhashi, and Thalhammer-Reyo, and further in view of Shannon et al., Genome research, Vol. 13, p. 2498-2504, 2003 (hereafter "Shannon") and in view of *Presentation of Biospice*, DARPA BioComp, May 2002 (hereafter "Biospice").

Applicants respectfully traverse the rejections.

A.   <u>Claims 1-5 and 20-23</u>

Applicants' claim 1 recites:

1.   A system for improved modeling of a biological system that comprises a plurality of chemical reactions, the system comprising:
         a modeling component having a graphical user interface for accepting user commands and input to construct or modify a model of the biological system;
         a simulation engine conducting a simulation of the model by accepting as input the model of the biological system and generating as output dynamic behavior of the biological system until the occurrence of a predefined simulation termination condition; and
         an analysis environment in communication with the simulation engine, the analysis environment
                 interfacing with data acquisition hardware that gathers data from an experiment, and
                 using the output of the simulation engine to control a property of the experiment, the output representing the dynamic behavior of the biological system at a completion of the simulation.

In order to better claim the invention, Applicants amend claim 1 to clarify that the output of the simulation which is used to control the experiment represents the dynamic behavior of the system <u>at a completion of the simulation</u>. Applicants further amend claim 1 to clarify that the simulation is carried out <u>until the occurrence of a predefined simulation termination condition.</u>

Applicants respectfully urge that Sauro, Kurata, and Funhashi, and Thalhammer-Reyo alone or in any reasonable combination, do not disclose or suggest at least an analysis environment that interfaces with data acquisition hardware and *uses the output of a simulation engine to control a property of an experiment* where *the output represents the dynamic behavior of the biological system <u>at a completion of the simulation</u>.*

In Applicants' previous Response dated June 16, 2010, Applicants argued that Sauro, Kurata, and Funhashi, alone or in combination, do not disclose or *using the output of the simulation engine to control a property of the experiment*. Hence, Sauro, Kurata, and Funhashi, alone or in combination, do not disclose or suggest *using the output of a simulation engine to control a property of an experiment* where *the output represents the dynamic behavior of the biological system <u>at a completion of the simulation</u>*.

The Examiner does not dispute this argument in the present Office Action. Instead, the Examiner argues that Thalhammer-Reyo cures the factual deficiencies of Sauro, Kurata, and Funhashi. Applicants respectfully disagree. Specifically, the information that Thalhammer-Reyo uses is gathered <u>at the wrong time</u>.

The Examiner argues that Thalhammer-Reyo discloses *using the output of the simulation engine to control a property of the experiment* at pages 10-11 (Office Action at pages 7-8). In the cited passages, Thalhammer-Reyo is describes the two types of variables which may be used within a "Simulated Virtual Model." Thalhammer-Reyo states that two types of variables are available: a "one-valued variable," and a "two-valued variable." The one-valued variables can take a single value, which represents a quantity derived from a simulation (Thalhammer-Reyo at paragraph 4, pages 9-10). The two-valued variables may take two distinct values: a first value corresponding to the quantity derived from the simulation, and a second value which represents a quantity of a corresponding entity measured in a particular biological sample (Thalhammer-Reyo at paragraph 4, pages 9-10, and paragraph 6, page 10).

Thalhammer-Reyo notes that, using a two-valued variable, it is possible to compare the measured value and the simulated value with reference to a particular inference criteria, and "take specified actions when the inference criteria are met" (Thalhammer-Reyo at paragraph 4, page 10). Such actions may include, for example, causing a valve for a component feed to be more or less open or closed, and the activation or deactivation of model pathways being simulated.

In order to expedite prosecution, Applicants amend claims 1 and 20 to clarify that the output of the simulation engine which is used to control the experiment *represents the dynamic behavior of the biological system <u>at a completion of the simulation</u>*. Applicants respectfully urge that Thalhammer-Reyo, even in combination with the other cited references, does not disclose or suggest this feature of claim 1.

In contrast to the present claims, which carry out a simulation to completion and then use the results of the simulation to influence an experiment, Thalhammer-Reyo is limited to maintaining a 1:1 correspondence between an <u>ongoing</u> simulation and an <u>ongoing</u> experiment. Thalhammer-Reyo specifically states that:

> Whenever <u>during the simulation</u> the values of any combination of any number of
> said monitored simulated variables, which are specific for each particular process
> design, reach certain values, then the programs pass control signals through the
> appropriate control auxiliary structures in the controller interfaces, which ...

control the flow of inputs and regulate the operation of the bioreactor, which is
being monitored <u>in a continuous manner</u>.

(Thalhammer-Reyo at page 10, paragraph 6, emphasis added)

Thalhammer-Reyo's system has limited capabilities. For example, the two-variable
model described in Thalhammer-Reyo is limited to modifying a bioreactor to ensure that the
processes occurring in the bioreactor correspond directly to the simulation which is <u>presently</u>
being carried out. Because the simulation attempts to hold entity quantities in the bioreactor to
the same level as in the simulation at the present time (thereby achieving a 1:1 correspondence
between the simulation and the bioreactor), Thalhammer-Reyo's system is not capable of using
<u>conclusions</u> drawn from the simulation to yield a better experiment, as is possible in the present
application.

For example, assume that carbon nanotubes are to be grown. Using the methods and
systems described in the present application, several simulations could be carried out to
completion with different combinations of variables (such as, for example, temperature). After
the simulations are completed, the end results (such as the number and quality of the nanotubes)
could be compared programmatically and the optimal environmental variables could be selected.
For example, the system may determine that a temperature of 102 degrees results in a better
quantity/quality of nanotubes than does a 100 degree temperature. The system may then use the
<u>results</u> of the simulation to control an in-situ experiment to grow the nanotubes. Because the
<u>results</u> of the simulation are used to control the experiment, a better experiment can be carried
out.

In contrast, Thalhammer-Reyo maintains a 1:1 correspondence between an ongoing
simulation and an ongoing experiment. Accordingly, Thalhammer-Reyo does not use the
information gained from following simulation to its conclusion; instead, Thalhammer-Reyo is
only capable of carrying out instructions such as, for example, "the simulation calls for see X
grams of entity Y at time T, but fewer grams are present. Increase the amount of entity Y until
X grams are achieved," or "the simulation says that X grams of entity Y should be present by
now, so activate microwell M." While this may allow a simulation to stay on the same footing

as an experiment, it does not provide the advantages of learning from the <u>conclusions</u> of the simulation to carry out a better experiment.

Whereas the present claims carry out a simulation <u>to completion</u> and then use the results of the simulation to influence the experiment, Thalhammer-Reyo is limited to maintaining a 1:1 correspondence between an ongoing simulation and an ongoing experiment. There is no disclosure or suggestion in Thalhammer-Reyo to ***use the output of a simulation engine to control a property of an experiment*** where ***the output represents the dynamic behavior of the biological system <u>at a completion of the simulation</u>***.

Furthermore, one of ordinary skill in the art would not be motivated to modify Thalhammer-Reyo to use the <u>results</u> of the simulation upon <u>completion</u> to control a property of the experiment, because Thalhammer-Reyo is not concerned with improving the experiment. Instead, Thalhammer-Reyo merely describes a way to <u>control</u> an experiment according to the specific prescriptions of a predefined model. There is no suggestion in any of the cited references to use the <u>results</u> of a simulation to improve an experiment, as is possible in the present claims.

For at least the reasons set forth above, Applicants urge that Sauro, Kurata, Funhashi, and Thalhammer-Reyo alone or in any reasonable combination, do not disclose or suggest at least ***using the output of a simulation engine to control a property of an experiment*** where ***the output represents the dynamic behavior of the biological system <u>at a completion of the simulation</u>***, which is present in claim 1. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 1 be withdrawn.

Claims 2-5 depend from independent claim 1 and, as such, incorporate all of the features of claim 1. Claims 2-5 are therefore allowable for at least the same reasons as claim 1. For at least the reasons set forth above, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 2-5 be withdrawn.

Independent claim 20 relates to a system that uses a simulation engine to generate an expected result of a chemical reaction as an output of the simulation engine. Claim 20 includes ***using the output of the simulation engine to control a property of the experiment, <u>the output</u>***

representing the expected result of the chemical reaction at a completion of the simulation. As discussed above with respect to claim 1, Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest at least that the output used to control a property of the experiment represents the expected result <u>at a completion of the simulation</u>.

Claims 21-23 depend from claim 20, and therefore include each and every feature of claim 20. Accordingly, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 20-23 be withdrawn.

B.   Claims 8-11, 14-17, 26-29, and 32-35

Applicants' claim 8 recites, among other features:

> performing a simulation of a model of a biological process until the occurrence of a predefined simulation termination condition to generate dynamic behavior of the modeled biological process; and
> providing an indication that data gathered at the conclusion of an experiment and the generated dynamic behavior at a completion of the simulation differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount.

Applicants have previously argued that Sauro, Kurata, and Funhashi do not disclose or suggest the comparison of generated dynamic behavior from a simulation to data gathered from an experiment. The Examiner does not dispute this argument in the present Office Action, and instead argues that Thalhammer-Reyo discloses this feature at page 11.

However, as noted above, Thalhammer-Reyo is not performing such a comparison with data gathered at the <u>conclusion</u> of an experiment and generated dynamic behavior measured at the <u>completion</u> of a simulation. The passage on page 11 describes comparison and control that takes place both <u>during simulation</u> and <u>during the experiment</u>. This is not what is recited in claim 8, which requires that the indication results from the comparison of *data gathered <u>at the conclusion of an experiment</u> and the generated dynamic behavior <u>at a completion of the simulation</u>*.

In view of the above, Applicants respectfully submit that Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 8. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 8 be withdrawn.

Claims 9-11 depend from independent claim 8 and, as such, incorporate all of the features of claim 8. Therefore, for at least the reasons set forth above with respect to claim 8, Applicants respectfully urge that the above 35 U.S.C. §103(a) rejection of claims 9-11 be withdrawn.

Applicants' claim 14 is an "article of manufacture" claim corresponding to claim 8. Claim 14 includes: *computer-readable instructions for providing an indication that data gathered __at a conclusion of an experiment__ and the generated dynamic behavior __at a completion of the simulation__ differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount*.

Applicants respectfully urge that Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 14 for at least the same reasons as described above in relation to claim 8. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 14 be withdrawn.

Claims 15-17 depend from independent claim 14 and, as such, incorporate all of the features of claim 14. Therefore, for at least the reasons set forth above with respect to claim 14, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 15-17 be withdrawn.

Applicants' claim 26 recites, among other features, *providing an indication that data gathered __at a conclusion of an experiment__ and the generated expected result __at a completion of the simulation__ differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated expected result is greater than the predetermined amount*

Independent claim 26 generally corresponds to claim 8, except that claim 26 recites a "model of a chemical reaction" where claim 8 recites a "model of a biological system." Applicants respectfully urge that Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest at least *providing an indication that data gathered at a conclusion of an experiment and the generated expected result at a completion of the simulation differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated expected result is greater than the predetermined amount*, which is present in claim 26.

As discussed above with respect to claim 8, neither Sauro, Kurata, Funhashi nor Thalhammer-Reyo compare *data gathered at a conclusion of an experiment* to *a generated expected result* at a completion of a simulation of a chemical reaction. For at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 26. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 26 be withdrawn.

Claims 27-29 depend from independent claim 26 and, as such, incorporate all of the features of claim 26. Therefore, for at least the reasons set forth above with respect to claim 26. Applicants respectfully request that the above 35 U.S.C. §102(a) rejection of claims 27-29 be withdrawn.

Applicants' claim 32 is an "article of manufacture" claim corresponding to claim 26. Claim 32 includes: *computer-readable instructions for providing an indication that data gathered at a conclusion of an experiment and the generated expected result at a completion of the simulation differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated expected result is greater than the predetermined amount*.

For at least the reasons set forth above with respect to claim 26, Applicants respectfully urge that Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 32.

Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 32 be withdrawn.

Claims 33-35 depend from independent claim 32 and, as such, incorporate all of the features of claim 32. Therefore, for at least the reasons set forth above with respect to claim 32, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 32-35 be withdrawn.

C.   Claims 37-39

Claim 37 was rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro in view of Kurata, Funhashi, Thalhammer-Reyo, Shannon, and BioSpice. Applicants respectfully traverse this rejection.

Claim 37 depends from claim 1, and therefore includes each feature of claim 1. As noted above with respect to claim 1, Sauro, Kurata, Funhashi, and Thalhammer-Reyo do not disclose or suggest at least *using the output of a simulation engine to control a property of an experiment* where *the output represents the dynamic behavior of the biological system at a completion of the simulation*, which is present in claim 1. The addition of Shannon and BioSpice fails to cure the factual deficiencies of Sauro, Kurata, Funhashi, and Thalhammer-Reyo with respect to disclosing or suggesting this feature of claim 1.

Shannon describes Cytoscape, an application for "integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework" (Shannon at Abstract). However, Shannon is entirely silent with respect to an *analysis environment interfacing with data acquisition hardware,* and *using the output of a simulation engine to control a property of an experiment* where *the output represents the dynamic behavior of the biological system at a completion of the simulation*, as included in claim 1.

Biospice is generally directed to an application to develop "a physically-grounded, molecular understanding of bacterial stress response," "an infrastructure suitable for rapid deduction of pathway dynamics," and "a theoretical and computational infrastructure [to] store,

relate and model the data at different levels of abstraction" (Biospice at "Goals"). BioSpice is silent with respect to an ***analysis environment interfacing with data acquisition hardware,*** and ***using the output of a simulation engine to control a property of an experiment*** where ***the output represents the dynamic behavior of the biological system <u>at a completion of the simulation</u>,*** as included in claim 1.

For at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, Thalhammer-Reyo, Shannon, and BioSpice, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 37. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 37 be withdrawn.

Claim 38 depends from claim 8, and therefore includes each and every feature of claim 8. Claim 39 depends from claim 14, and therefore includes each and every feature of claim 14. As noted above with respect to claims 8 and 14, Sauro, Kurata, Funhashi, and Thalhammer-Reyo, alone or in any reasonable combination, do not disclose or suggest each and every feature of claims 8 and 14. The addition of Shannon and Biospice fails to cure the deficiencies of Sauro, Kurata, Funhashi, and Thalhammer-Reyo with respect to disclosing or suggesting all of the features of claims 38 and 39.

Shannon describes Cytoscape, an application for "integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework" (Shannon at Abstract). However, Shannon is entirely silent with respect to ***providing an indication that data gathered <u>at a conclusion of an experiment</u> and the generated dynamic behavior <u>at a completion of the simulation</u> differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount***, as included in claims 8 and 14.

Biospice is generally directed to an application to develop "a physically-grounded, molecular understanding of bacterial stress response," "an infrastructure suitable for rapid deduction of pathway dynamics," and "a theoretical and computational infrastructure [to] store, relate and model the data at different levels of abstraction" (Biospice at "Goals"). BioSpice is silent with respect to ***providing an indication that data gathered <u>at a conclusion of an</u>***

***experiment** and the generated dynamic behavior <u>at a completion of the simulation</u> differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount*, as included in claims 8 and 14.

For at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, Thalhammer-Reyo, Shannon, and BioSpice, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claims 38-39. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 38-39 be withdrawn.

CONCLUSION

In light of the above, Applicants respectfully urge that all of the pending claims are in condition for allowance. Should the Examiner feel that a teleconference would expedite the prosecution of this application, the Examiner is urged to contact the Applicants' attorney at 617-573-4700.

Please charge any shortage or credit any overpayment of fees to our Deposit Account No. 12-0080, under Order No. MWS-111RCE3. In the event that a petition for an extension of time is required to be submitted herewith, and the requisite petition does not accompany this response, the undersigned hereby petitions under 37 C.F.R. §1.136(a) for an extension of time for as many months as are required to render this submission timely. Any fee due is authorized to be charged to the aforementioned Deposit Account.

Dated: December 13, 2010   Respectfully submitted,

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